IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Francis J. GILES et al. Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/729,387 Group Art Unit: 1614

Filed: December 8, 2003

For: PHARMACEUTICAL COMBINATIONS AND METHODS FOR THE TREATMENT OF LEUKEMIA

BRIEF ON APPEAL UNDER 37 C.F.R. §41.37

MAIL STOP: APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed May 16, 2008, attached herewith is Appellants' Brief on Appeal, pursuant to 37 CFR §41.20(b)(2). This is an appeal from the decision of the Examiner finally rejecting claims 1, 3-15, and 17-60 in the Office Action issued January 16, 2008.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(1) REAL PARTY IN INTEREST

The application is assigned of record to Shire BioChem Inc. (now doing business as Shire Canada Inc.), who is the real party in interest herein. The assignment is recorded in Reel 015440/Frame 0931.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected: 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64;

Claims allowed: None;

Claims canceled: 2-6, 8, 11-13, 16, 23, 24, 33-38, and 46-51;

Claims withdrawn: None;

Claims objected to: None;

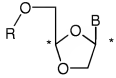
Claims on Appeal: 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64. A copy of the claims on appeal is provided in the attached Claim Appendix.

(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments have been filed subsequent to the Final Office Action issued January 16, 2008.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

Appellants' claims on appeal include three independent claims, i.e., claims 1, 14, and 15. As set forth in claim 1, Appellants' invention is directed to a pharmaceutical composition comprising at least one active compound of formula (I):



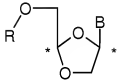
(I)

or a pharmaceutically acceptable salt thereof,

wherein B is cytosine, and R is H; and

the Bcr-Abl tyrosine kinase inhibitor imatinib mesylates. See, e.g., page 4, lines 8-23, page 7, line 31, page 9, lines 29-31, and page 18, lines 13-17 In this composition, the compound of formula (I), or pharmaceutically acceptable salt thereof, and the Bcr-Abl tyrosine kinase inhibitor are present in a ratio of 1:5 to 1:2. See, e.g., treatment schemes e) and f) in the "in vivo studies" at pages 25-27 and Figs. 12-14.

Similarly, as set forth in claim 14, Appellants' invention is directed to a pharmaceutical combination comprising at least one active compound of formula (I):



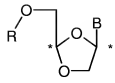
(I)

or a pharmaceutically acceptable salt thereof,

wherein B is cytosine, and R is H; and

the Bcr-Abl tyrosine kinase inhibitor imatinib mesylates. See, e.g., page 4, lines 8-23, page 7, line 31, page 9, lines 29-31 In this combination, the compound of formula (I), or pharmaceutically acceptable salt thereof, and the Bcr-Abl tyrosine kinase inhibitor are present in a ratio of 1:5 to 1:2. See, e.g., treatment schemes e) and f) in the "in vivo studies" at pages 25-27 and Figs. 12-14.

Additionally, as set forth in claim 15, Appellants' invention is directed to a method of treating a patient having leukemia comprising administering to the patient a therapeutically effective amount of a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof,

wherein B is cytosine, and R is H; and

the Bcr-Abl tyrosine kinase inhibitor imatinib mesylates. See, e.g., page 11, lines 13-30, and page 13, lines 28-31. In this method, the compound of formula (I), or pharmaceutically acceptable salt thereof, and the Bcr-Abl tyrosine kinase inhibitor are present in a ratio of 1:5 to 1:2. See, e.g., treatment schemes e) and f) in the "in vivo studies" at pages 25-27 and Figs. 12-14.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The ground of rejection on Appeal is: whether claims 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64 are unpatentable under 35 USC §103(a) in view of Chu et al. (WO 96/07413) in combination with the article by Giles et al., the article by Drucker et al., the article by Fang et al., and the article by Topaly et al.

(7) APPELLANTS' ARGUMENTS

I. Rejection under 35 USC 103(a) in view of Chu et al. (WO 96/07413) in combination with the abstract by Giles et al., the article by Drucker et al., the article by Fang et al., and the article by Topaly et al.

Claims 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-62 are rejected as allegedly being obvious in view of Chu et al., Giles et al., Drucker et al., Fang et al. and Topaly et al. This rejection is respectfully traversed.

Chu et al., Giles et al., and Drucker et al. are relied on in the rejection for disclosures of the use of (-)-L-OddC or imatinib mesylates (STI-571) for the treatment of leukemia and dosages for such agents in the treatment of leukemia.

Chu et al. (WO 96/07413) disclose the use of L-OddC for the treatment of cancer. See page 5, lines 17-27. The exemplified cancers include leukemia. See page 6, lines 18-28.

The article by Giles et al., (J. Clin. Oncology, 19, 3, (2001), pp762-771), discloses the results of a study in which patients with advanced leukemia were treated with troxacitabine (i.e., (-)-L-OddC). Of the 42 patients treated, 31 had acute myeloid leukemia (AML), 6 had myelodysplastic syndrome (MDS), 4 had acute lymphocytic leukemia (ALL), and 1 had chronic myeloid leukemia in blastic phase (CML-BP). The troxacitabine was administered in courses by continuous infusion for 30 minutes daily for 5 days with a starting dose of $0.72/m^2$/day. In the study, 8 mg/m^2/day of troxatyl for 5 days was determined to be the MTD and the recommended dosage for further studies.

Giles et al. note that prior nucleoside compounds developed for cancer treatment, like ara-C (cytarabine), were in the D-configuration, whereas troxacitabine has the L-configuration. See page 762. Additionally, Giles et al. disclose that the "pharmacokinetic behavior of troxacitabine is substantially different from that of other nucleoside analogs possessing a D configuration." See page 770, left column

Drucker et al. disclose the results of a study on STI571, a Bcr-Abl tyrosine kinase inhibitor. As noted by Drucker et al., Bcr-Abl is an enzyme that "is present in virtually all cases of chronic myeloid leukemia" and in 20% of acute lymphoblastic leukemia. The study investigated the treatment of patients with myeloid blast crisis and lymphoid blast crisis using STI571. The daily dosages ranged from 300 to 1000 mg. Drucker et al. state that the results of the study demonstrates that STI571 "as a single" is well tolerated and has substantial activity. See page 1041 right column.

These references do not disclose or suggest treating leukemia with a combination of (-)-L-OddC and STI571. In the rejection, it is argued that Chu et al. disclose using L-OddC in combination with other agents. It is further argued the Appellants' specification

acknowledges that STI571 has been used in combination with other agents. See discussion at page 3, lines 4-9 regarding studies involving STI571 in combination with cytarabine. However, the cited prior art provides no suggestion that the combination of (-)-L-OddC and STI571 would achieve synergistic results.

Conversely, Appellants' specification clearly discloses that the combination of (-)-L-OddC and STI-571 exhibits synergistic results. The disclosures of Chu et al., Giles et al., and Drucker et al. are devoid of any suggestion or expectation that combining (-)-L-OddC and STI-571 will achieve synergistic effects.

At pages 25-28 of the specification, Appellants' present the results of *in vivo* studies concerning the treatment of mice injected with KBM-5 and KBM-5R tumor cells. At the bottom of Table 1 (page 27), results are presented for Troxatyl alone at 10 mg/kg/day, Troxatyl alone at 25 mg/kg/day, STI-571 alone at 50 mg/kg/day, Troxatyl at 10 mg/kg/day plus STI-571 at 50 mg/kg/day, and Troxatyl at 25 mg/kg/day plus STI-571 at 50 mg/kg/day (see schemes b)-f) at page 26).

As shown In Table 1, for Troxatyl alone at 10 mg/kg/day, the increased life span, ILS%, (mean survival time of treated animals minus that of control animals over the mean survival time of the control group) is 50.90% (ILS exceeding 25% indicates significant antitumor activity), and for STI-571 alone at 50 mg/kg/day, the ILS is 8.95%. However, when the animals were treated with Troxatyl at 10 mg/kg/day plus STI-571 at 50 mg/kg/day, the ILS increased to **80.06**%.

Similarly, for Troxatyl alone at 25 mg/kg/day, ILS is 71.33%, and, as noted before, for STI-571 alone at 50 mg/kg/day, the ILS is 8.95%. However, when the animals were treated with Troxatyl at 25 mg/kg/day plus STI-571 at 50 mg/kg/day, the ILS increased to **125.17**%.

Additionally, again referring to the bottom of Table at page 27,none of the treatment schemes in which Troxatyl or STI-571 were administered alone showed any Long Term Survivors (LTS). Conversely, in the treatment scheme for Troxatyl at 10 mg/kg/day plus STI-571 at 50 mg/kg/day, there was 1 long term survivor, and in the treatment scheme for Troxatyl at 25 mg/kg/day plus STI-571 at 50 mg/kg/day, there was 3 long term survivors.

With respect to synergistic results, the rejection relies on the disclosures of Fang et al. and Topaly et al. The Examiner argues that Fang et al. disclose that, in *in vitro* tests,

cotreatment of certain cell lines with STI-571 and the agents Ara-C, etoposide and doxorubicin yielded increased apoptosis. See page 2252, right column. Additionally, the Examiner argues that Topaly et al. discloses that, in *in vitro* tests, STI-571 exhibited synergism with respect to apoptosis induced by cytarabine (Ara-C), mafosfamide and etoposide.

Yet, the disclosures of Fang et al. and Topaly et al. do not establish that one skilled in the art would expect STI-571 to exhibit synergy with every anti-leukemia agent. Nothing within these two disclosures suggests that STI-571 will interact favorably with all other anti-leukemia agents, rather than having an adverse interaction. Similarly, these two disclosures do not suggest that STI-571 will exhibit synergy with all other anti-leukemia agents, regardless of the mechanism of apoptosis induces by such agents.

The structures of cytarabine (Ara-C), etoposide, doxorubicin and mafosfamide are all clearly distinguishable from that of (-)-L-OddC. Of these four agents, only cytarabine has a nucleoside structure. While (-)-L-OddC does possess a nucleoside-like structure, it has a dioxolane ring rather than a typical sugar ring and does not have the pendant hydroxy groups of the typical sugar ring, such as possessed by cytarabine. Furthermore, as noted above, (-)-L-OddC (troxacitabine) is recognized in the art as having a substantially different pharmacokinetic behavior than that of ara-C. See the discussion above regarding the article by Giles et al.

In the Office Action of January 16, 2008, it is argued stated that "The prior art discloses that… and further demonstrates that STI-571 has a synergistic effect when combined with other agents." However, these references clearly do not make such a sweeping conclusion. One or ordinary skill in the art would not conclude or expect that, based on the limited *in vitro* studies on STI-571 in combination with 4 other agents, that STI-571 will exhibit synergistic effects when combined with any other anti-leukemia agent. Moreover, the disclosures of Fang et al. and Topaly et al. clearly would not lead one of ordinary skill in the art to expect that STI-571 will exhibit synergy with an anti-leukemia nucleoside agent having the L-configuration (rather than the D-configuration of ara-C) and having a dioxolane structure, as in the case of (-)-L-OddC.

For the reasons discussed above, one of ordinary skill in the art would not make the general assumption that STI-571 will be expected to exhibit synergy with any anti-leukemia

agent, regardless of the latter's mechanism of action or its structure. Nor will one of ordinary skill in the art make the general assumption that STI-571 will interact synergistically, rather than additively or even adversely, with all other anti-leukemia agents.

In view of the above remarks, it is respectfully submitted that of Chu et al., Giles et al., and Drucker et al., taken alone or in combination or further in combination with Fang et al. and/or Topaly et al., fail to render obvious Appellants' claimed invention. Reversal of the rejection is respectfully requested.

(8) CONCLUSION

For all of the above reasons, it is urged that the decision of the Examiner finally rejecting claims 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64, on appeal, is in error and should be reversed.

Respectfully submitted,

/Brion P. Heaney/

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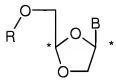
Brion P. Heaney
Registration No. 32,542

Filed: July 16, 2008

CLAIMS APPENDIX

1. (Previously Presented): A pharmaceutical composition comprising at least one active compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

B is cytosine, and

R is H; and

the Bcr-Abl tyrosine kinase inhibitor imatinib mesylate,

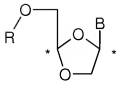
wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof and said Bcr-Abl tyrosine kinase inhibitor are present in a ratio of 1:5 to 1:2.

7. (Previously Presented): The pharmaceutical composition according to claim 1, wherein the compound of formula I is (-)-β-L-Dioxolane-Cytidine.

9. (Previously Presented): The pharmaceutical composition according to claim 1, wherein the compound of formula I is substantially in the form of the (-) enantiomer.

10. (Previously Presented): The pharmaceutical composition according to claim 1, wherein said compound of formula (I) is at least 97% free of the corresponding (+) enantiomer.

14. (Previously Presented): A pharmaceutical combination comprising at least one active compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

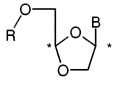
B is cytosine, and

R is H; and

the Bcr-Abl tyrosine kinase inhibitor imatinib mesylate;

wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof and the Bcr-Abl tyrosine kinase inhibitor are present in a ratio of 1:5 to 1:2.

15. (Previously Presented): A method of treating a patient having leukemia comprising administering to said patient a therapeutically effective amount of a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof,

wherein

B is cytosine, and

R is H; and

the Bcr-Abl tyrosine kinase inhibitor imatinib mesylate,

wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof and said Bcr-Abl tyrosine kinase inhibitor are administered at a ratio of 1:5 to 1:2.

17. (Previously Presented): The method according to claim 15, wherein said patient is suffering from acute myelogenous leukemia.

18. (Previously Presented): The method according to claim 15, wherein said patient is suffering from chronic myelogenous leukemia in blastic phase.

19. (Previously Presented): The method according to claim 15, wherein said patient has refractory/relapsed leukemia.

20. (Previously Presented): The method according to claim 15, wherein said patient has refractory / relapsed leukemia and said patient has been previously treated with imatinib mesylate.

21. (Previously Presented): The method according to claim 15, wherein said patient has refractory/relapsed leukemia, said patient has been previously treated with imatinib mesylate, and said patient is resistant to imatinib mesylate.

22. (Previously Presented): The method according to claim 15, wherein said patient has refractory/relapsed leukemia and said patient has been previously treated with imatinib mesylate, wherein the compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

25. (Previously Presented): A pharmaceutical composition according to claim 1, further comprising at least one pharmaceutically acceptable carrier or excipient.

26. (Previously Presented): A method according to claim 15, wherein said patient is suffering from chronic myelogenous leukemia.

27. (Previously Presented): A method according to claim 15, wherein said patient is suffering from acute lymphocytic leukemia.

28. (Previously Presented): A method according to claim 15, wherein said patient is suffering from chronic lymphocytic leukemia.

29. (Previously Presented): A method according to claim 15, wherein said patient is suffering from hairy cell leukemia.

30. (Previously Presented): A method according to claim 15, wherein said patient is suffering from acute myelogenous leukemia, acute myeloid leukemia, chronic myelogenous leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, acute lymphocytic leukemia, hairy cell leukemia, myelodysplastic syndrome or chronic myelogenous leukemia in blastic.

31. (Previously Presented): A pharmaceutical composition according to claim 1, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof is at least 95% free of the corresponding (+) enantiomer.

32. (Previously Presented): A pharmaceutical composition according to claim 1, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof is at least 99% free of the corresponding (+) enantiomer.

39. (Previously Presented): A method according to claim 15, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to said patient at a dose between 1 mg/m^2 and 8 mg/m^2, and said Bcr-Abl tyrosine kinase inhibitor is administered to said patient at a dose between 0.1 gm/m^2 and 30 gm/m^2.

40. (Previously Presented): A method according to claim 15, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to said patient at a dose between about 1 mg/m^2 and about 8 mg/m^2, and said Bcr-Abl tyrosine kinase inhibitor is administered to said patient at a dose between 0.1 gm/m^2 and 6 gm/m^2.

41. (Previously Presented): A method according to claim 15, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof and said Bcr-Abl tyrosine kinase inhibitor are administered sequentially.

42. (Previously Presented): A method according to claim 15, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof and said Bcr-Abl tyrosine kinase inhibitor are administered simultaneously in a separate pharmaceutical formulations.

43. (Previously Presented): A method according to claim 15, wherein said

compound of formula (I) or a pharmaceutically acceptable salt thereof and said Bcr-Abl tyrosine kinase inhibitor are administered simultaneously in a combined pharmaceutical formulation.

44. (Previously Presented): A combination according to claim 14, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof and said Bcr-Abl tyrosine kinase inhibitor are in separate pharmaceutical formulations.

45. (Previously Presented): A combination according to claim 14, wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof and said Bcr-Abl tyrosine kinase inhibitor are in a combined pharmaceutical formulation.

52. (Previously Presented): A method according to claim 15, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

53. (Previously Presented): A method according to claim 17, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

54. (Previously Presented): A method according to claim 18, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

55. (Previously Presented): A method according to claim 19, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

56. (Previously Presented): A method according to claim 26, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

57. (Previously Presented): A method according to claim 27, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

58. (Previously Presented): A method according to claim 28, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

59. (Previously Presented): A method according to claim 29, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

60. (Previously Presented): A method according to claim 30, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

61. (Previously Presented): A method according to claim 39, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

62. (Previously Presented): A method according to claim 40, wherein said compound of formula (I) is (-)-β-L-Dioxolane-Cytidine.

63. (Previously Presented): A method according to claim 52, wherein β-L-OddC is administered at 6mg/m^2 over 30 minutes per day on days 1 to 5 and imatinib mesylate is administered at 1gm/m^2 over 2 hours daily on days 1 to 5.

64. (Previously Presented): A method according to claim 52, wherein β-L-OddC is administered at 5mg/m^2 over 30 minutes per day on days 1 to 5 and imatinib mesylate is administered at 12gm/m^2 over 2 hours daily on days 1 to 3.

EVIDENCE APPENDIX

Not Applicable.

RELATED PROCEEDINGS APPENDIX

Not Applicable.